

# INFLAMMATORY PSEUDOTUMORS OF THE LUNG: IMPORTANCE OF RECOGNITION AND DIFFERENTIATION FROM NEOPLASTIC AND GRANULOMATOUS PROCESSES

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**Two cases of inflammatory pseudotumors of the lung are reported and the literature is reviewed. The lesions are commonly discovered incidently in asymptomatic young persons and are characterized by a solitary, homogeneous, well-circumscribed mass composed of the major kinds of inflammatory elements in various proportions. The lesion should be differentiated from true neoplasms and common granulomas. Resection of the lesion results in permanent cure.**

Inflammatory pseudotumors of the lung are rare lesions, commonly characterized by a persistent or slowly growing, solitary lung mass that often masquerades as a neoplasm but proves to be a nonspecific inflammatory process (confirmed by histology), composed predominantly of plasma cells and/or histiocytes.<sup>1-12</sup> Confusion about such an entity has been generated in the past because of the lack of an identifiable causative agent and the multitude of names applied to the lesion based upon its highly variable histologic features.<sup>1-13</sup> It is important to recognize inflammatory pseudotumors of the lung as benign lesions and differ-

entiate them from true neoplasms and common granulomatous processes because, hitherto, no death has been attributed directly to such inflammatory pseudotumors.

Two cases of inflammatory pseudotumors of the lung with different clinical courses and histologic features are presented. In one case the lesion was removed 17 years ago and the patient is still living and well, while in another case, the lesion was not removed but the patient has been closely observed during the past seven years.

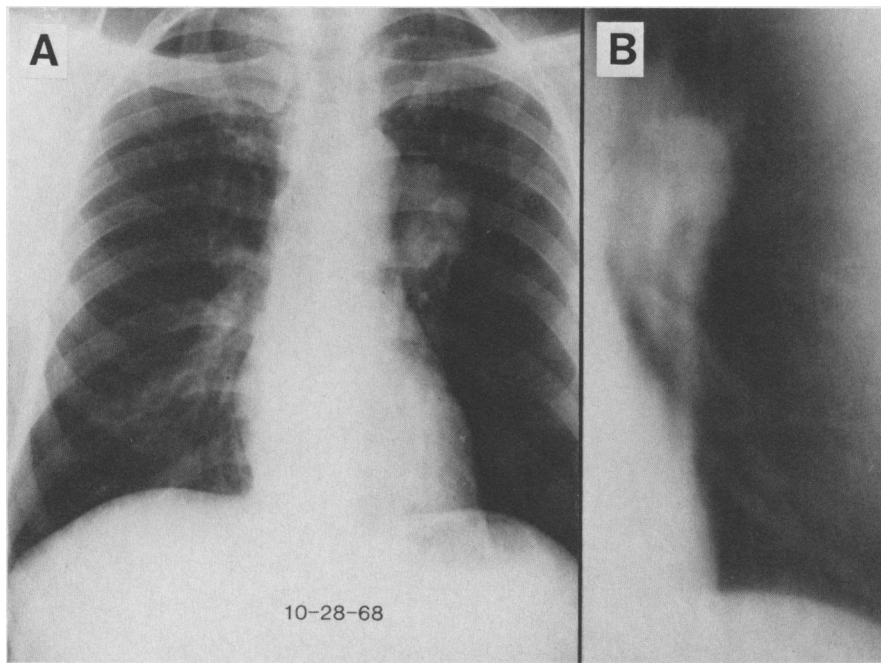
## CASE REPORTS

### Case 1

A 34-year-old man was admitted to the hospital for paranoid behavior of approximately two months' duration. A large left-sided hilar mass with the appearance of a neoplasm was seen on chest x-ray film taken on admission (Figure 1A). The patient's schizophrenic reaction was treated with drugs while a workup of the lung lesion was performed. The left-sided hilar mass measured 6 cm in diameter, and was rather homogeneous, well demarcated, and round on posteroanterior film (Figure 1A) but was obviously lobulated on tomogram (Figure 1B). Skin tests and sputum cultures for tuberculosis and fungal infections were negative. Sputum cytologies, bronchoscopy, and mediastinoscopy were negative for malignancy. An exploratory left-sided thoracotomy was then performed revealing a large

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**Figure 1. A round, well-demarcated mass in the left hilum (A, posteroanterior film) is revealed on the chest radiograph that is seen as lobulated on tomogram (B)**

mass in the anterior segment of the left upper lobe, which protruded into the mediastinum at the level of the lung hilum on the left side. A left-sided pneumonectomy was carried out because a frozen section was reported as suspected malignant disease.

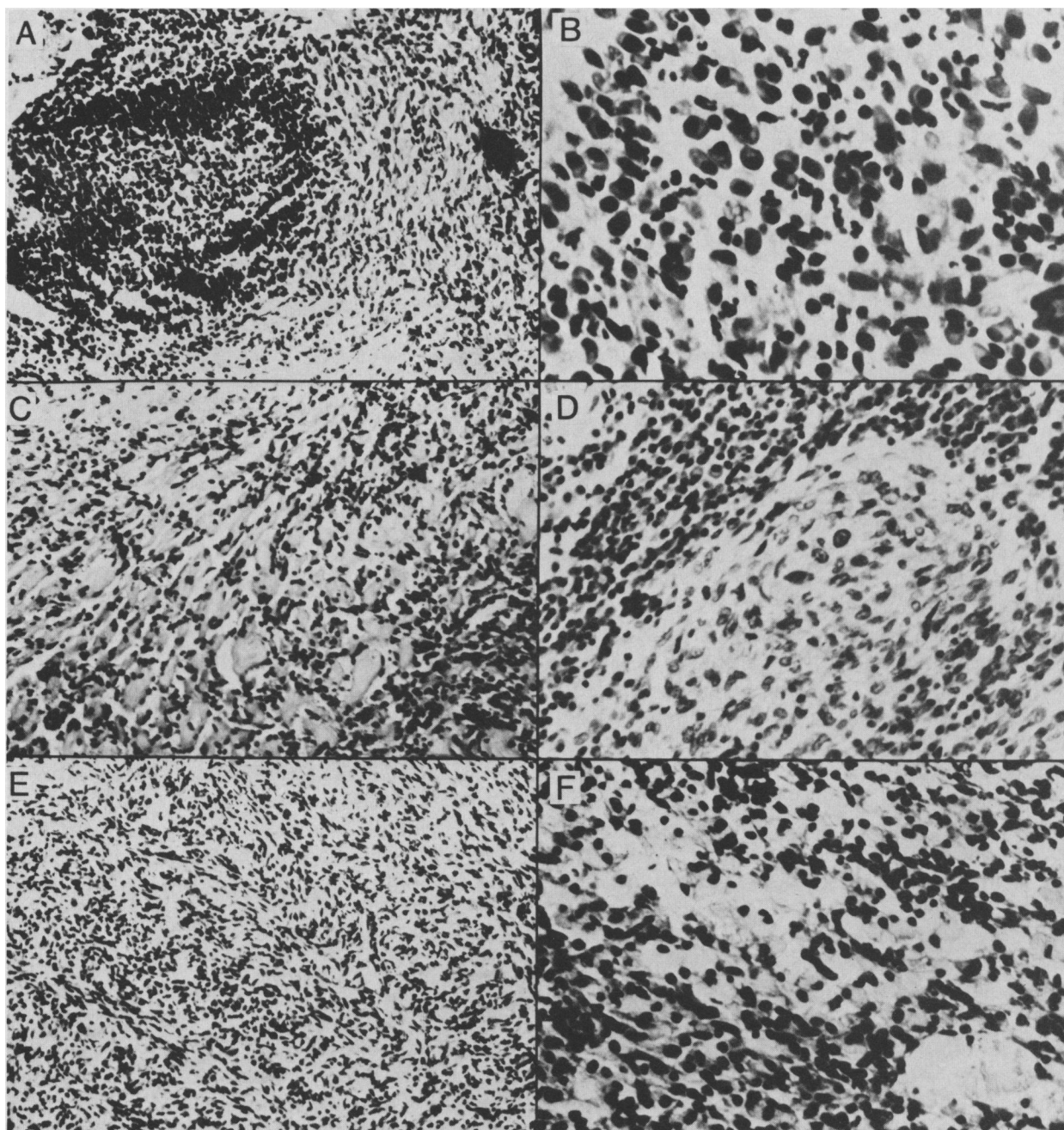
On gross examination the mass in the lung on the left side was slightly lobulated, well defined but not encapsulated, measuring 6 cm in its greatest dimension, and located subpleurally without invasion of the pleura. The cut surfaces were white-grey with scattered yellow and brown spots and small foci of cystic degeneration. The consistency was firm to rubbery. Microscopically, a combination of varieties of the following histologic features was present (Figure 2): lymphocytic infiltrates with occasional germinal centers (Figure 2A), focal neutrophilic and eosinophilic infiltrates, massive aggregates of mature plasma cells with easily identifiable Russell bodies (Figure 2B), granulation tissue composed of capillaries and fibrous tissue (Figure 2C), sheets of epithelioid histiocytes with occasional multinucleated giant cells (Figure 2D), bundles of spindle-shaped histiocytes and collagen arranged in storiform patterns (Figure 2E), loose and dense fibrous

tissue, old hemorrhages with hemosiderin deposit and cholesterol granuloma formation and rare, small focal calcifications and small cysts walled-off by chronic inflammatory cells (Figure 2F). The above process seemed to arise from the lung parenchyma and to expand peripherally to the adjacent lung tissue. Special stains and cultures of the lung failed to yield any microorganisms.

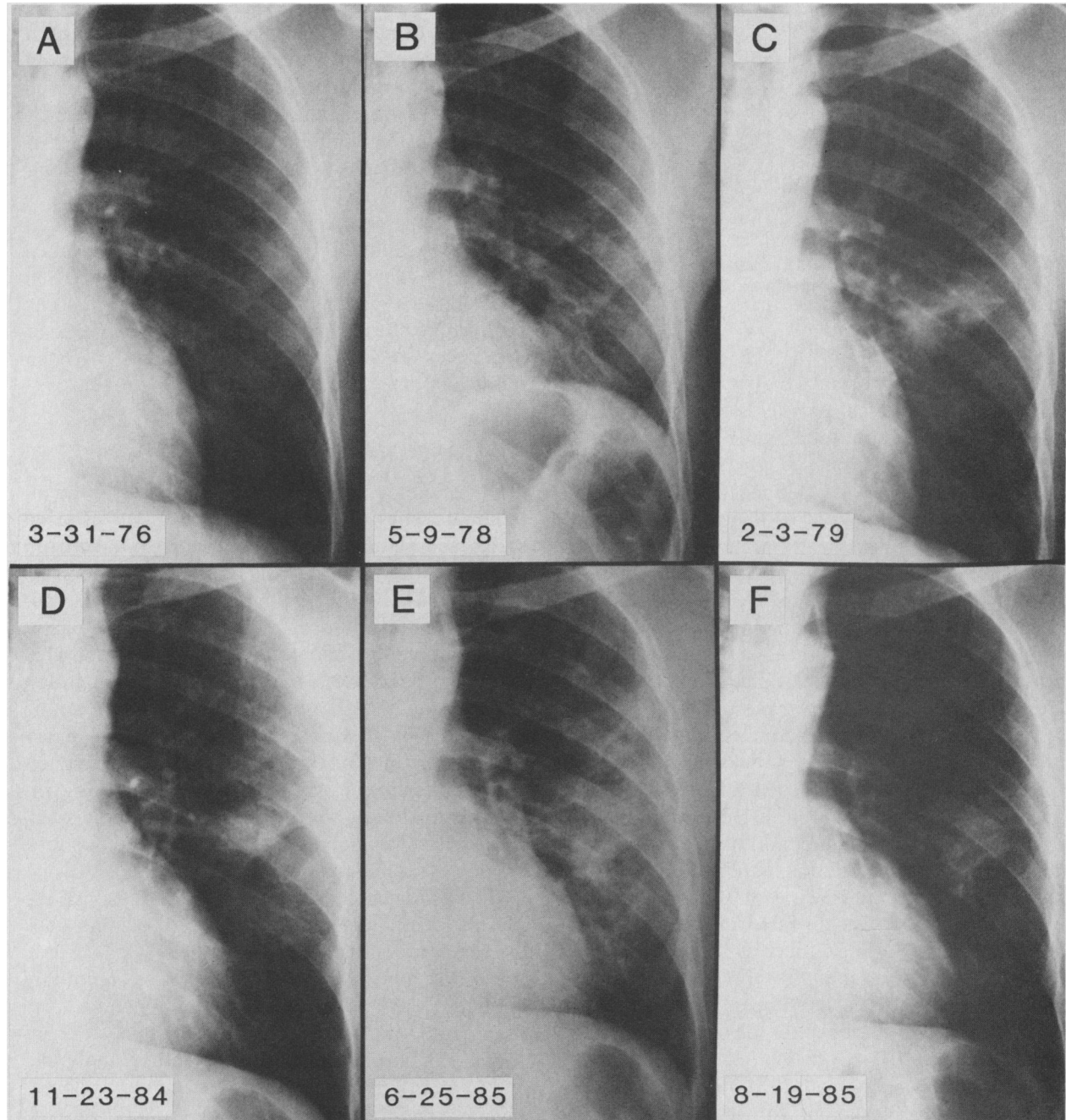
The patient recovered from the surgery uneventfully. Subsequently, his schizophrenic reaction was brought under control. Seventeen years later, the patient is living and well, free from recurrent lung lesion.

## Case 2

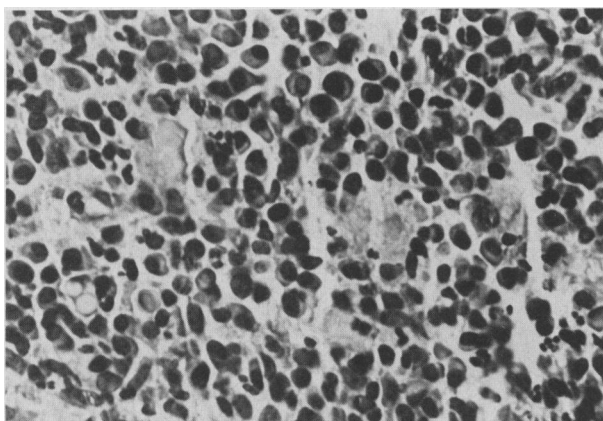
A 32-year-old male construction worker, who has been a binge drinker and two pack-a-day smoker for 15 years, first developed dull, continuous pain in the lower chest on the left side associated with shortness of breath and mild fever in May 1978. Inhomogeneous opacities in the lingula segment of the left upper lobe with elevation of the left-sided hemidiaphragm, consistent with pneumonia, were revealed on a chest radiograph (Figure 3B). A previous chest film, taken in March



**Figure 2. A wide spectrum of histologic features characterizing the inflammatory pseudotumors in case 1: (A) lymphocytic infiltrate with germinal center (A & E,  $\times 150$ ), (B) aggregate of mature plasma cells admixed with acute inflammatory cells (H & E,  $\times 600$ ), (C) fibrosis and vascular spaces resembling sclerosing hemangioma (H & E,  $\times 150$ ), (D) epithelioid cells (H & E,  $\times 300$ ), (E) spindle-shaped histiocytes with collagen fibers arranged in storiform pattern (H & E,  $\times 150$ ), and (F) xanthomatous area with large foam cells (H & E,  $\times 300$ )**



**Figure 3. A series of chest x-ray films of case 2 taken at different intervals. The evolution of the lung lesion and complication of pneumonia (B and E) are revealed**



**Figure 4. The lung lesion in case 2 composed primarily of mature plasma cells with easily identifiable Russell bodies**

1976, was entirely normal (Figure 3A). He was treated with antibiotics and his symptoms much improved. However, in February 1979, the patient came back with sore throat, cough, chest pain, and subjective fever. A poorly defined elliptical opacity in the superior segment of lingula division of the left upper lobe was seen on chest radiograph (Figure 3C). He was again treated with antibiotics, and his symptoms subsided and the lesion shrunk.

In November 1984, the patient returned with a cough productive of blood-streaked sputum. The recurrence of the elliptical opacity in the left upper lobe was seen on chest radiograph (Figure 3D). The opacity was inhomogenous and the outline somewhat irregular. He was again placed on antibiotics. No change in the lesion was seen on a repeat chest radiograph in December 1984. The patient was doing quite well until June 1985, when he again developed cough productive of yellow-green sputum. Flaring of the opacity in the left upper lobe was revealed on chest radiograph (Figure 3E). The enlarged lesion became ill-defined and seemed to involve both anterior and lingula segments of the left upper lobe. He was then readmitted to the hospital for further evaluation and treatment.

The patient was a well-developed and well-nourished, young, black man with no positive physical signs and laboratory findings on the latest admission. Even the lungs were clear to percussion and auscultation. A skin test for tuberculosis and sputum cultures for bacteria and fungi were all negative; the same results had been obtained sev-

eral times before. Bronchoscopy showed inflammation at the orifice of the lingua segment with partial obstruction. A biopsy of the lingua segment was obtained.

The biopsy specimen was composed primarily of sheets of mature plasma cells admixed with a few eosinophils and neutrophils (Figure 4). Russell bodies could be identified with no difficulty. The plasma cells were stained positive for both  $\kappa$  and  $\lambda$  light chains of immunoglobulin by the peroxidase-antiperoxidase method, indicating their polyclonal nature.

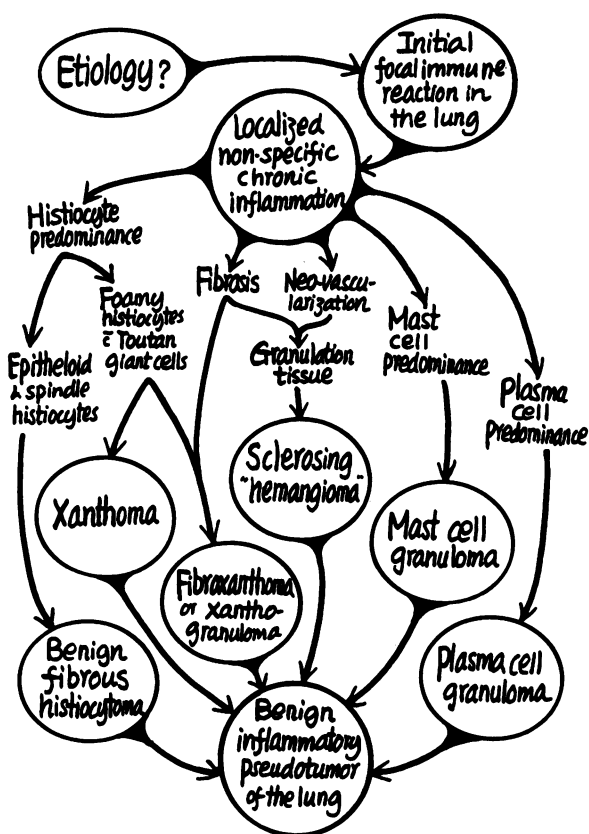
The acute process subsided after antibiotic therapy. A follow-up chest radiograph was taken in August 1985; the persistence of the opacity in the superior segment of the lingula (Figure 3F) was seen on the chest film. The patient has been free of symptoms since the last discharge, and has been followed closely by the clinic.

## DISCUSSION

No etiologic agent has been identified in the inflammatory pseudotumor of the lung. Special stains and cultures for microorganisms have been negative in all reported cases, including the present two patients.<sup>1-13</sup> As the disease process is usually chronic and localized, the causative agent might initiate the inflammatory responses and then disappear from the lesion while the inflammation persists. On the other hand, the agent might not be detectable by the present techniques. The highly variable histologic features suggest that the lesion could be elicited by more than one kind of agent, but this might not be true because the whole spectrum of histologic features could be found in a single case as in case 1.

The principal cells involved in the response are plasma cells and histiocytes. When plasma cells are the predominant cells in the lesion as in case 2, the term "plasma cell granuloma" is commonly applied.<sup>1,2,6,11-13</sup> When histiocytes become predominant, "benign fibrous histiocytoma," "xanthoma," "fibroxanthoma" or "xanthogranuloma" are adopted.<sup>7-10</sup> The entity of "pulmonary sclerosing hemangioma" described in the literature is most likely a variant of the inflammatory pseudotumors.<sup>8,14-17</sup> Some lesions may contain a large number of mast cells, and thus the entity is designated as "mast cell granuloma."<sup>18</sup> As all the above histologic variants can be found in a single





**Figure 5.** Diagram of a unifying hypothesis of benign inflammatory pseudotumors of the lung: various terminology reflects only the emphasis of the predominant elements in a localized, nonspecific, chronic inflammatory process

lesion as demonstrated in case 1 (Figure 2), they should be grouped together as a single entity (Figure 5).

Inflammatory pseudotumors of the lung occur more commonly in young persons: two thirds under the age of 30 years and one third under the age of 18 years. This entity is twice as common in women as in men.<sup>1-13</sup> Most cases are asymptomatic and are discovered incidentally as in case 1. The most common symptoms are cough, chest pain, fever, and dyspnea, all well demonstrated in case 2. The periodic flare-up of the lesion in case 2, accompanied by respiratory and constitutional symptoms, was apparently related to the pneumonia that developed as a consequence of bronchial obstruction secondary to the compression by the inflammatory pseudotumor. As soon as the pneumonia was resolved after antibiotic treat-

ment, the original mass lesion reappeared.

The most common radiographic finding observed in over two thirds of cases is a solitary, homogeneous, well-circumscribed, spherical or oval mass of 2 to 3 cm in diameter.<sup>1-13</sup> Rarely does the mass reach a size as large as 13 cm.<sup>11</sup> Multiple or lobulated nodules are noted only occasionally. Cavitation and endobronchial involvement are uncommon but were present in case 2. Obvious calcification of the untreated lesion is extremely rare. Nonetheless, a recent report revealed that the lesion became calcified in three patients after radiation therapy.<sup>13</sup> The mass is usually soft and yellow-white with occasional small brown spots of old punctate hemorrhages. The mass is discrete but not truly encapsulated.

Most inflammatory pseudotumors become stationary after the initial acute phase is over, which is usually mild and overlooked. Their differentiation from the true neoplasms and granulomatous inflammation of known etiology is important but difficult to determine, and can be certain only after biopsy and cultures. Every effort should be made to rule out the possibility of tuberculous and fungal infections. The polyclonal nature of the plasma cells should be confirmed by immunohistochemical or immunocytochemical means to rule out extraosseous plasmacytoma.

The natural history of inflammatory pseudotumors of the lung remains uncertain. Although no death has been attributed directly to the disease, and resection of the lesion results in permanent cure (case 1) the fate of the mass lesion remains unknown when left untouched. It might persist for a long time (case 2), or might heal spontaneously by fibrosis. The longer the lesion persists, the greater the chance for the following two possible complications: (1) partial or complete obstruction of bronchus because of endobronchial involvement or extrinsic compression by the mass, predisposing to either pneumonia or atelectasis,<sup>19-21</sup> or (2) the development of true neoplasm, particularly malignant lymphoma, because long-term stimulation of lymphocytes in chronic inflammation might lead to emergence of autonomous clone of neoplastic lymphocytes as is often observed in lymphomatoid granulomatosis and Sjögren's syndrome.<sup>22</sup> Therefore, if pneumonia recurs, or the lesion suddenly grows rapidly as in case 2, surgical resection or radiation therapy should be indicated.

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BRIEF SUMMARY  
**DIABINESE® (chlorpropamide)**  
TABLETS, USP

## CONTRAINDICATIONS

- DIABINESE is contraindicated in patients with:
1. Known hypersensitivity to the drug.
  2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

## WARNINGS

**SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY**

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 [supp. 2]:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in over-all mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of DIABINESE and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

## PRECAUTIONS

## General

**Hypoglycemia:** All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of DIABINESE and the latter may also diminish glucagonogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.

**Loss of control of blood glucose:** When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

## ADVERSE REACTIONS

**Hypoglycemia:** See PRECAUTIONS section.

**Gastrointestinal Reactions:** Cholestatic jaundice may occur rarely; DIABINESE should be discontinued if this occurs. Gastrointestinal disturbances are the most common reactions: nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose related and may disappear when dosage is reduced.

**Dermatologic Reactions:** Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABINESE; if skin reactions persist the drug should be discontinued.

Porphyrria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas. Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.

**Hematologic Reactions:** Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia and eosinophilia have been reported with sulfonylureas.

**Metabolic Reactions:** Hepatic porphyria and disulfiram-like reactions have been reported with DIABINESE.

**Endocrine Reactions:** On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality.

## DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with DIABINESE or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, and to detect secondary failure. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.

**Initial Therapy:** 1. The mild to moderately severe, middle-aged, stable, non-insulin-dependent diabetic patient should be started on 250 mg daily. Older patients should be started on smaller amounts of DIABINESE, in the range of 100 to 125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable non-insulin-dependent diabetic patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a 50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of three to five days to obtain optimal control. More frequent adjustments are usually undesirable.

**Maintenance Therapy:** Most moderately severe, middle-aged, stable non-insulin-dependent diabetic patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 MG DAILY SHOULD BE AVOIDED.

## HOW SUPPLIED

Blue, "D" shaped, scored tablets in strengths of 100 mg, tablet code 393; (100's, NDC# 0663-3930-66; 500's, NDC# 0663-3930-73; and 100 unit dose of 10 x 10, NDC# 0663-3930-41) and 250 mg, tablet code 394; (100's, NDC# 0663-3940-66; 250's, NDC# 0663-3940-71; 1000's, NDC# 0663-3940-82; 100 unit dose of 10 x 10, NDC# 0663-3940-41; and 30's D-Pak, NDC# 0663-3940-30).

**RECOMMENDED STORAGE:** Store below 86°F (30°C).

**CAUTION:** Federal law prohibits dispensing without prescription.

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